

Canadian Agency for  
Drugs and Technologies  
in Health

Agence canadienne  
des médicaments et des  
technologies de la santé



## T E C H N O L O G Y   O V E R V I E W

**HTA**

Issue 34  
December 2007

Overview of Thiazide Diuretics as  
First-Line Treatment for Hypertension



*Supporting Informed Decisions*

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**Cite as:** Tran K, Ho C, Noorani HZ, Cimon K, Hodgson A, Coyle D, Coyle K, Myers MG, Wright JM. *Overview of thiazide diuretics as first-line treatment for hypertension* [Technology overview number 34]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, the Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

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CADTH is funded by Canadian federal, provincial, and territorial governments.

Legal Deposit – 2007  
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ISSN: 1203-9012 (print)  
ISSN: 1481-4501 (online)  
O0343 – December 2007

PUBLICATIONS MAIL AGREEMENT NO. 40026386  
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**Canadian Agency for Drugs and Technologies in Health**

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We thank Lisa Hum for her assistance in creating this overview from a longer report authored by Tran *et al.*

This overview is based on a technology report commissioned by CADTH: Tran K, Ho C, Noorani HZ, Cimon K, Hodgson A, Coyle D, Coyle K, Myers MG, Wright JM. *Thiazide diuretics as first-line treatment for hypertension: meta-analysis and economic evaluation*. [Technology report number 95]. Canadian Agency for Drugs and Technologies in Health; 2007.

## Thiazide Diuretics as First-Line Treatment for Hypertension: Meta-analysis and Economic Evaluation

### Technology and Condition

Thiazide diuretics (TZD) chlorthalidone, hydrochlorothiazide, indapamide, and metolazone for primary hypertension (at least 140 mm Hg systolic or 90 mm Hg diastolic blood pressure).

### Issue

Despite their demonstrated clinical effectiveness and low cost, the rate of first-line TZD use in newly treated hypertensive patients remains lower than that of angiotensin-converting enzyme (ACE) inhibitors,  $\alpha$ -blockers (AB), angiotensin II receptor blockers (ARB),  $\beta$ -blockers (BB), and calcium channel blockers (CCBs). There is also uncertainty about the evidence supporting blood pressure targets.

### Methods and Results

A systematic review and a meta-analysis were conducted. Clinical and quality-of-life impacts were derived from 44 RCTs. Evidence of targeting blood pressure was derived from nine trials. TZDs reduced stroke events relative to ACE inhibitors and reduced heart failure events relative to CCB, but total cardiovascular and cerebrovascular events were not significantly different. For all patient groups, TZDs represent the least costly therapeutic option and are the second most effective option behind CCB.

### Implications for Decision Making

- **Compelling evidence suggests that TZDs are effective first-line agents.** TZDs are comparable with ACE inhibitors, BB, and CCB in reducing the risks of many adverse outcomes, including mortality. No evidence comparing TZDs with AB or ARB was found. Overall differences in quality of life were not evident.
- **TZDs are least costly.** Based on a simulation model of treating newly diagnosed hypertensive patients 55 and 65 years of age, TZDs represent the least costly option and the second most effective option behind CCBs. CCBs are cost-effective for those willing to pay from \$400,000 to \$3 million for a quality-adjusted life-year, depending on the patient's risk of future disease.
- **First-line TZDs will curb increased expenditures.** If TZDs are used first-line, future increases in spending will be lower and, for some provinces, may decrease in the short term.
- **No compelling evidence for lower blood pressure targets was identified.** It is unclear if intensive lowering of blood pressure below the standard target (140/90 mm Hg) can significantly alter health outcomes important to patients.

This summary is based on a comprehensive health technology assessment available from CADTH's web site ([www.cadth.ca](http://www.cadth.ca)): Tran K, Ho C, Noorani HZ, Cimon K, Hodgson A, Coyle D, Coyle K, Myers MG, Wright JM. *Overview of thiazide diuretics as first-line treatment for hypertension.*

# 1 Introduction

Hypertension, which is persistently elevated arterial blood pressure (BP), is a public-health concern in developed countries. It is common, asymptomatic, detectable, usually treatable, and can lead to lethal complications if unidentified or untreated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) gradually increase in men and women from 18 to 50 years of age.<sup>1</sup> After the age of 50 years, SBP continues to increase throughout life while DBP tends to level or drop off. The most common causes of death in patients with hypertension are due to effects on the heart, cardiovascular (CV) system, and kidney.<sup>2</sup>

Hypertension is the most common diagnosis in Canada. The number of primary diagnoses at physicians' offices reached up to 21.3 million in 2004, a 24% increase from that in 2001.<sup>3</sup> Of those diagnosed with hypertension, 80% received drug prescriptions. The Canadian Heart Health Survey indicates that approximately 22% of Canadians 18 to 70 years old have hypertension, and 75% of Canadians with hypertension are younger than 65 years old.<sup>4</sup> The lowering of BP can be achieved by a combination of healthy lifestyle and pharmacological treatment. Classes of antihypertensive drugs include thiazide diuretics (TZDs), angiotensin-converting enzyme (ACE) inhibitors, adrenergic blocking agents [including  $\alpha$ -blockers (ABs) and  $\beta$ -blockers (BBs)], calcium channel blockers (CCBs), and angiotensin-II receptor blockers (ARBs).

TZDs have been suggested as first-line agents for the management of hypertension. In Canada, available thiazide and thiazide-like diuretic drugs include chlorthalidone (Apo-Chlorthalidone<sup>®</sup>), hydrochlorothiazide (Apo-Hydro<sup>®</sup>, Novo-Hydrazide, PMS-Hydrochlorothiazide), indapamide (Apo-Indapamide<sup>®</sup>, Gen-Indapamide, Lozide<sup>®</sup>, Novo-Indapamide, PMS-Indapamide), and metolazone (Zaroxolyn<sup>®</sup>).

The mechanisms for the lowering of BP by thiazides are incompletely understood. TZDs inhibit sodium chloride re-absorption from the kidney. TZDs also induce a loss of potassium (hypokalemia) and an increase of uric acid in the serum. Significant hypokalemia occurs infrequently. When it does occur, it can usually be corrected by using potassium-sparing diuretics or potassium supplements. Other side effects of TZDs are hypomagnesemia, hypercalcemia, hyperurecemia (which can cause gout), hyperglycemia, hyperlipidemia, and sexual dysfunction. Low-dose therapy with TZDs is less likely to produce these abnormalities. TZDs also lower calcium excretion in the urine, so they are used to prevent calcium-containing kidney stones. The reduced calcium excretion is associated with increased bone density in postmenopausal women.<sup>5</sup>

Canadian utilization data for antihypertensive drug classes are available by province, although this information is not restricted to hypertension. New Brunswick and British Columbia reported an average unit cost of \$0.13. The estimated expenditure per person ranged from \$16 (in Prince Edward Island) to \$52 (in Manitoba). Compared with other classes of antihypertensive drugs, TZDs were the least expensive in terms of expenditure per person. Conversely, the percentage of prescriptions for TZD was the second lowest among the drug classes.

The rate of thiazide use in hypertensive patients remains lower than that of other antihypertensive drug classes. There is a need to systematically evaluate the health outcomes and relative costs of first-line thiazide use in hypertensive therapy compared with other drug classes in patients with or without co-morbidities.

## 2 Objectives

The aim of this health technology assessment is to evaluate the evidence for the clinical effects and the economic implications of TZDs when used as a first-line treatment for hypertension. This assessment is intended to inform those who must decide on an optimal choice of antihypertensive drug therapy in a patient diagnosed with hypertension for the first time. The economic implications of treating a typical newly diagnosed 55- or 65-year-old patient, with no additional risk factors such as heart disease, abnormal blood cholesterol, or diabetes, are examined. The effects of reducing blood pressure below the standard target of 140/90 mm Hg are evaluated.

The objective was accomplished by addressing three questions:

- Does the use of first-line TZDs change morbidity and mortality as compared with no treatment or placebo and other first-line antihypertensive drug classes for treatment of the following populations:
  - patients with uncomplicated primary hypertension (primary prevention)
  - patients with primary hypertension and co-morbidities (primary prevention)
  - patients with primary hypertension and an existing CV event or disease (secondary prevention)?
- What are the economic implications of the use of first-line TZDs in the treatment of hypertension as compared with no treatment or placebo and other first-line antihypertensive drug classes in newly diagnosed 55- or 65-year-old patients with no significant additional risk factors?
- Does aiming for BP targets lower than 140/90 mm Hg result in a difference in morbidity and mortality as compared with the standard target of 140/90 mm Hg in patients with hypertension?

## 3 Clinical Review

### **Methods**

Published literature was obtained by cross searching Medline, EMBASE, BIOSIS Previews, PubMed, and the Cochrane Library. Searches were performed to retrieve controlled trials, meta-analyses, and systematic reviews. Grey literature was obtained by searching the web sites of health technology assessment and related agencies and those of professional associations. Google and other Internet search engines were used to search for additional information.

Studies were included if they were randomized clinical trials (RCTs), involved participants with primary hypertension (i.e., SBP  $\geq$ 140 mm Hg or DBP  $\geq$ 90 mm Hg at baseline), and examined the outcomes of total mortality, CV, and cerebrovascular (CRV) events, kidney disease, change in SBP and DBP, and quality of life (QoL). Included RCTs must also have compared TZDs versus placebo, no treatment, or active treatment; have a study duration  $\geq$ 1 year; and measure BP at baseline and at  $\geq$ 1 points post-baseline. To address lower BP targets, included RCTs must randomize patients to aim for different BP targets. Two reviewers independently screened titles and abstracts. Data were extracted by three reviewers independently. Disagreements were resolved by consensus. Quality assessment was performed by two reviewers using the Jadad scale.<sup>6</sup> Scores of 3 to 5 were considered to be high while scores  $\leq$ 2 were low.

Dichotomous data were combined using relative risk (RR) and the relative risk difference (RRD). The number needed to treat (NNT) was calculated based on the RR. Continuous data with variances were combined using a weighted mean difference (WMD) method. Where no variance was reported, a value was imputed. Where the quantitative pooling of results was appropriate, the random effects model was used to compute treatment efficacy. The heterogeneity of treatment effect between trials was detected using the common chi-square test with  $p < 0.10$  indicating significant heterogeneity. A qualitative systematic review was performed for QoL outcomes.

## Results

### a) Trials related to TZDs versus placebo and other drug classes

A total of 6,167 citations compared TZDs versus placebo or other drug classes. Of these, 145 reports describing 44 unique trials (26 clinical trials and 18 trials having QoL data only) were selected for inclusion. Of the 26 clinical trials, eight had QoL data. Quality assessment showed that one trial<sup>7</sup> scored 5, three trials<sup>8-10</sup> scored 4, six trials<sup>11-16</sup> scored 3, 11 trials<sup>17-27</sup> scored 2, and five trials<sup>28-32</sup> scored 1 on the Jadad scale. The allocation concealment was unclear in all trials.

**TZDs versus placebo or no treatment:** Seventeen trials compared TZDs with placebo. Six trials<sup>11,13,22,25,26,29</sup> included elderly hypertensive individuals, three trials<sup>8,12,19</sup> had stroke or transient ischemic attack survivors with normal or high BP, and the other eight trials<sup>9,14,15,17,18,24,27,33</sup> had patients with a broader range of ages, with mild to moderate hypertension, and without comorbidities. The BP goals for the treatment groups were  $<140$  to  $160$  mm Hg for SBP and  $<90$  to  $100$  mm Hg for DBP.

Compared with placebo or no treatment, TZDs significantly reduced the risks of all-CV events, stroke, myocardial infarction (MI), CRV, heart failure (HF), all-cause death, and CV death. The risk reduction observed with TZDs for all-CV events, including coronary heart disease (CHD), MI, and CV death, was significant in higher mortality risk populations such as seniors. There was no significant difference between treatment groups for CHD, renal failure (RF), and withdrawals due to adverse events (AEs). More seniors withdrew from TZD treatment than from placebo, and there was a statistically significant risk reduction for CHD among the elderly. The WMD for SBP and DBP were all negative and statistically significant for the overall population and for the subgroup populations. QoL with TZDs and QoL with placebo were compared in nine trials.<sup>10,14,25,27,34-38</sup> Two trials<sup>10,34</sup> showed no significant differences between treatment and placebo, whereas seven trials<sup>14,25,27,35-38</sup> indicated a higher incidence of male sexual dysfunction in the TZD group.

**TZDs versus ACE inhibitors:** TZDs and ACE inhibitors were compared in three trials<sup>7,13,28</sup> for stroke and all-cause deaths and in two trials<sup>7,28</sup> for all-CV events, CHD, and HF. Risk reduction was not significantly different between treatments for all-CV events, CHD, HF, all-cause deaths, and withdrawal due to AEs. The risk of stroke was significantly lower with TZDs than placebo. The WMDs for SBP and DBP were not statistically significantly different between treatments. TZDs were associated with male sexual dysfunction in two trials,<sup>37,39</sup> and ACE inhibitors were associated with better QoL in two trials.<sup>40,41</sup> Four trials<sup>42-45</sup> showed no differences between treatments.

**TZDs versus BBs:** Four trials<sup>14,22,30,31</sup> showed no statistically significant differences between treatments for all-CV events, CHD, stroke, CV death, all-cause death, and withdrawal due to AEs. The WMD for SBP and DBP were not statistically significant. No differences in QoL between treatments were reported in seven trials,<sup>34,41,42,46-49</sup> three trials<sup>37,38,50</sup> showed a higher incidence of male sexual dysfunction with thiazide or chlorthalidone, and one trial<sup>30</sup> showed that patients on BBs

experienced a higher incidence of QoL disturbances. One trial<sup>39</sup> showed that both treatments were associated with sexual dysfunction.

**TZDs versus CCBs:** Six trials compared the clinical outcomes of TZDs and CCBs.<sup>7,16,20,21,23,32</sup> Risk reduction was similar between treatment groups for all-CV events, CHD, MI, stroke, CRV, RF, all-cause deaths, and withdrawal due to AEs. The DBP was also not statistically significantly different between treatments, although the SBP was significantly lower with CCBs. The risk of HF was significantly less (29%) with TZD treatment relative to therapy with CCBs. QoL results showed no significant differences between treatments in four trials.<sup>32,41,46,51</sup> TZDs or CCBs were linked to male sexual dysfunction in three trials.<sup>16,37,39</sup>

**TZDs versus ARBs:** No studies comparing the clinical effects of TZDs and ARBs were identified. No difference was found in QoL between candesartan and thiazide in two trials.<sup>44,52</sup> One trial<sup>53</sup> found that losartan, which is an ARB, improved QoL.

#### **b) Clinical trials related to lower BP target**

A total of 1,379 citations were identified, of which 45 reports describing nine unique trials were selected. The trials included patients with diabetes,<sup>54-56</sup> kidney disease,<sup>57-61</sup> or hypertension without mention of co-morbidities.<sup>62</sup> Trials scored 1,<sup>55,58,63</sup> 2,<sup>56,59-61</sup> 3,<sup>57</sup> or 5<sup>64</sup> on the Jadad scale. Patients were randomized to achieve a moderate lowering of BP to <140/90 mm Hg or intensive lowering of BP to <130/80 mm Hg. Pharmacological treatment differed among and in trials.

The intensive lowering of BP below the standard target did not result in any significant reduction in risk of all-cause death, CV death, stroke, MI, or RF. No significant differences were observed in subgroup analyses. The intensive lowering of BP reduced SBP and DBP by 7.25 mm Hg and 5.33 mm Hg respectively, significantly more than that achieved by treating to the moderate target.

## **4 Economic Analysis**

### **Literature Search**

All electronic databases that were searched for the clinical objective were also searched for the economic objective, with the addition of the Health Economics Evaluations Database (HEED) and the use of a filter to restrict results to studies with economic components. The web sites of other professional associations were searched to obtain economic information.

Studies were included if they were reports of full economic evaluations that compared TZD monotherapy with  $\geq 1$  class of antihypertensive therapy or with no therapy. Included studies must assess the initial treatment of primary hypertension in an adult population. Studies related to specific disease subgroups were excluded. Of 1,740 studies identified, 16 were included in the literature review. TZDs were compared with BBs in 14 studies, ACE inhibitors or ARBs in 14 studies, and CCBs in 13 studies. Ten studies were cost-effectiveness analyses with outcomes of life-years gained,<sup>65-68</sup> deaths prevented,<sup>69,70</sup> CV events prevented,<sup>71,72</sup> control of BP,<sup>73</sup> or compliance.<sup>74</sup>

In seven cost-effectiveness studies, TZDs were considered to be the most cost-effective option. In two studies, BBs were considered to be more cost-effective.<sup>66,68</sup> Another study favoured the use of an ARB (losartan).<sup>75</sup> In two of the three cost-utility analyses incorporating quality adjusted life-years

(QALYs),<sup>76-78</sup> TZDs were the most cost-effective option. In two of three<sup>79-81</sup> cost-minimization analyses that assumed an equal benefit between treatment options, TZDs were the least costly initial therapy. In the other study, BBs were the least costly strategy, followed by TZDs. Thus, in most studies, TZDs were the most cost-effective initial treatment of hypertension. Where TZDs were not the most cost-effective, BBs or CCBs were more cost-effective. Although several economic evaluations were identified, none addressed the question that is relevant to this report from a Canadian perspective. Thus, the completion of a full economic evaluation was considered to be appropriate.

### **Primary Economic Evaluation**

The cost-effectiveness of treating newly diagnosed hypertension with TZDs versus alternative antihypertensive classes was assessed. Analyses were conducted for eight groups of patients based on combinations of the following characteristics: men or women, 55 or 65 years of age, and baseline SBP of 150 or 180 mm Hg. The base case scenario included non-smokers with no history of diabetes or left ventricular hypertrophy, with normal cholesterol and high-density lipoprotein (HDL) levels (5.0 and 1.3 respectively). A Markov decision model was used to estimate the long-term costs and QALYs associated with CV and CRV disease in the study populations. A 10-year time horizon with a cycle length of one year was chosen. All patients were assumed to start in a “well” state, which represents no previous additional CV or CRV events. The model was populated with the most appropriate estimates of transition probabilities, treatment effects, costs, and QoL. Differences among treatments were assessed by adjusting the transition probabilities using RRs.

The direct cost of drug therapy and the costs associated with the long-term complications of hypertension were incorporated in the model. All costs included in the model were Canadian. The analysis was conducted from the perspective of a provincial ministry of health. For the base case analysis, the costs and benefits were discounted at 5% per annum.<sup>82</sup> A sensitivity analysis was conducted with discounting at 0% and 3%.<sup>82</sup> Sensitivity analyses were conducted to assess the robustness of the study’s results to changing assumptions in the model: costs associated with complications, disutility associated with complications, and application of RRs associated with treatment of primary and secondary events.

#### **a) Results**

For all groups, TZDs were the least costly therapeutic option and the second-most effective option after CCBs. Thus, TZDs dominated BBs, ACE inhibitors or ARBs, and no therapy. CCBs were more effective in terms of greater QALYs than TZDs. The incremental cost-effectiveness ratio (ICER) per QALY gained for CCBs versus TZDs was >\$400,000 for all groups of patients. The ICER expressed per QALY gained for CCBs versus TZDs ranged from \$450,000 for men aged 65 years with a SBP of 180 mm Hg to \$1.1 million for men aged 55 years with a SBP of 150 mm Hg. The range was from \$400,000 for women aged 65 years with a SBP of 180 mm Hg to \$2 million for women aged 55 years with a SBP of 150 mm Hg. Thus, the ICER was higher in patients with a lower risk of hypertension-related events (younger and lower initial SBP). The results of the sensitivity analysis were similar to those of the primary analysis, with TZDs continuing to dominate BBs, ACE inhibitors or ARBs, and no treatment.

## 5 Limitations

The meta-analysis of clinical effectiveness assumed that antihypertensive treatments in each drug class were constant across trials. A step-care or combination therapy approach, however, was followed in most trials. The patient populations, BP goal, and the doses and drug types in each drug class differed among trials. When heterogeneity occurred, a subgroup analysis by age was conducted. Heterogeneity, however, might also result from a variation in methods. Most trials used a selected population that might not be generalizable. Thus, the results from this report should be interpreted with this in mind. Most trials were of low quality and had inadequate or unclear allocation concealment. Subgroup analysis based on trial quality was not always possible because of small numbers and inconsistent outcome reporting. This review could not determine the effect of TZDs on subpopulations with specific co-morbidities. Hypertensive patients often have co-morbidities, and most need more than one drug to achieve optimal BP control. The limitations of the QoL analyses included the use of non-standardized tools, subjective conclusion of unpublished data in some cases, non-blinding in trials, and lack of statistical analyses of some QoL outcome data. These limitations made it impossible to pool the data and derive a point estimate.

The economic evaluation was limited by a lack of head-to-head studies comparing all treatment options. Results were often based on indirect comparisons, which can lead to false inference. Although a sensitivity analysis was conducted to address the uncertainty around RR estimates, the uncertainty around other parameters could not be analyzed, because only point estimates were available for many parameters. Another limitation is that the study focussed on the impact of initial monotherapy and did not model the choice of switches in monotherapy or initiation of combination therapy. One reason for this is the lack of clinical trial data assessing the optimal secondary treatment options after monotherapy. Modelling beyond initial monotherapy would likely be based on weak assumptions. Second, it was unclear whether the analysis would incorporate secondary therapy as adopted in Canada or optimal secondary therapy that could be established. In some cases, the analysis adopted conservative assumptions that were biased against more effective treatment. It was assumed that patients would be equally adherent to therapies, which may lead to bias. Another limitation is that the study included only the outcomes directly related to hypertension and did not model other long-term conditions. Finally, the report included only disutility related to disease events. There was evidence from the clinical review that there may be differential QoL for patients on different therapies. It is unclear, however, whether differences found in the review would translate into different utility values.

## 6 Health System Implications

Although the number of prescriptions for TZDs increased between 2000 and 2006 in some Canadian provinces, the proportion in 2005-2006 for TZDs relative to other antihypertensive drug classes remains low (from 8% to 22%). Except for ABs, the use of other antihypertensive drug classes increased during the past five years. If prescribing trends continue as they have over the past five years, the expenditure for antihypertensive medications will increase yearly. On the other hand, results from a budget impact analysis showed that if antihypertensive therapy is started with TZDs instead of other therapeutic classes, the yearly increase in expenditure is reduced. For example, in BC, the projected impact on the budget for 2008-2009 is \$82 million, \$79 million, and \$69 million based on 5%, 10%, and 25% respective reductions in non-thiazide prescriptions and corresponding

increases in thiazide prescriptions. This is compared to a budget impact of \$85 million if there is no reduction in non-thiazide prescriptions and no corresponding increase in TZD prescriptions

The advent of newer antihypertensive drugs such as ACE inhibitors, adrenergic blocking agents, and CCBs leads to questions about the allocation of health care resources, because cost savings achieved through TZD therapy can be translated into health benefits from new effective but costly therapies (e.g., cancer care) for smaller populations. There are differences in TZD utilization patterns between provinces despite no difference in the evidence and costs of therapy.

## 7 Conclusion

TZD-based therapy is superior to placebo or no treatment in reducing the risks of all-CV and CRV events in patients with uncomplicated hypertension. No significant differences for all-CV and CRV-related morbidity and mortality were found when TZDs were compared with other antihypertensive medications. TZDs, however, were better in reducing the risk of stroke than ACE inhibitors and in reducing the risk of HF than CCBs.

The economic analysis found little difference between therapies in terms of effectiveness and found TZDs to be the most cost-effective initial therapy for patients in all study populations, unless society is willing to pay >\$400,000 for a QALY gained from the use of calcium channel blockers.

Evidence from a limited number of trials, most of which were of low quality, showed that the intensive lowering of blood pressure below the standard target of 140/90 mm Hg in patients with hypertension did not result in a difference in the risks of all-cause death, death related to cardiovascular events, and renal failure.

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